



Pupil responses in patients with COVID-19

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Abstract

Aim To compare pupillary responses in patients with Coronavirus disease-2019 (COVID-19) during active infection and at 3rd months post-infection.

Methods This study included 58 COVID-19 cases (mean age 47.23 ± 1.1 years). The scotopic, mesopic and photopic diameters were noted. Pupil diameters were noted at the 0, 1st, 2nd, 4th, 6th, 8th, and 10th seconds in reflex pupil dilation after the termination of a light. The average dilation speed was calculated at the 1st, 2nd, 4th, 6th, 8th, and 10th seconds. Pupil responses measured during COVID-19 infection and 3 months later were compared.

Results The mean scotopic and mesopic pupil diameter value of during COVID-19 infection was found lower than the 3rd month post-infection. ($p = 0.001$, $p = 0.023$; respectively). No statistically significant difference was found in the mean photopic pupil diameter and the mean pupil diameter at 0 s between measurements ($p > 0.05$, $p = 0.734$; respectively). The mean pupil diameter was significantly lower during COVID-19 infection at the 1st, 2nd, 4th, 6th, 8th and 10th seconds ($p < 0.01$, for each). The average dilation speed measurements at every second

measured were lower in during COVID-19 infection than the 3rd months later ($p = 0.001$; $p < 0.01$ for each).

Conclusions Pupil responses were found significantly different in COVID-19 cases when compared with the measurements taken three months later.

Keywords Autonomic neuropathy · COVID-19 · Pupil

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in severe acute respiratory syndrome [1]. The most commonly reported symptoms are fever, cough, myalgia or fatigue, and complicated dyspnea [2]. The SARS-CoV-2 enters the lungs, the most affected organ in this disease, through the angiotensin-converting enzyme (ACE)-2 receptor found in type II alveolar epithelial cells [3].

In addition, a report from China has shown that some patients did not suffer from respiratory symptoms but had neurologic signs and symptoms [4]. Glial cells and neurons of the central nervous system have been reported to express ACE-2 receptors, therefore, the brain becomes the potential target of the virus [5].

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The transneuronal transport of SARS-CoV through the olfactory bulb supports this hypothesis [6]. In a retrospective study from China, neurologic symptoms were observed in 36.4% of the hospitalized patients with COVID-19 infection [7]. Interestingly, a patient detected with COVID-19 virus in the cerebrospinal fluid has also been reported [8].

In COVID-19 cases, autonomic nervous system involvement is also possible [9]. Because one case report showed a case with COVID-19 displaying initial non-epileptic seizures and the association of the COVID-19 with autonomic dysfunction was emphasized in this report [10]. In the aforementioned case, EEG was normal and the sympathetic skin response was pathological, which is an objective sign for autonomic dysfunction. Inexplicable symptoms and signs may also be related to autonomic system involvement. Whether the examination of brainstem reflexes such as corneal reflexes and pupillary reflexes are useful for early detection of central nervous system (CNS) involvement is still unclear. However, since pupil functions are managed by the autonomic nervous system, the assessment of pupil function might be a useful test for determining autonomic dysfunction.

The aim of this study is to compare the results of the pupil responses during and three months later COVID-19 infection.

Methods

This study included 58 COVID-19 cases (diagnosis was confirmed by PCR test) who were hospitalized in July 2020. The study was approved by the ethics committee of the Prof. Dr. Cemil Tascioglu Education and Research Hospital under the principles of the Helsinki Declaration.

All participants provided written informed consent prior to undergoing all examinations. The participants were excluded from the study if they had situations that might interfere with the proper interpretation of pupillometry results. The exclusion criteria were determined as follows: (1) previous ocular surgery (2) ocular disease that may affect pupil function such as pseudoexfoliation syndrome, history of ocular trauma, congenital or acquired iris and pupil anomalies, anterior or posterior synechiae, uveitis, corrected distance visual acuity < 20/50 in the Snellen chart, glaucoma, grade 3–4 cataract, history of optic

neuropathy, retinal diseases that may affect pupil functions, permanent use of topical medications (3) systemic diseases that may affect pupil function such as multiple sclerosis, Parkinson's disease, Alzheimer's disease (4) patients with comorbidities that may affect autonomic functions such as chronic lung diseases, cardiovascular pathologies, hypertension, kidney diseases, diabetes mellitus, and obesity (5) systemic medications that may affect pupil function such as α -1 blocker (6) cases with desaturation without oxygen mask.

Firstly, eyelids were evaluated for the presence of ptosis. Then we evaluated pupil responses by the automated pupillometry function of the Sirius Topographer (CSO, Firenze, Italy) using Phoenix v2.1 software (Costruzione Strumenti Oftalmici, CSO, Firenze, Italy). All measurements were performed by the same experienced clinician during active COVID 19 infection and at the 3rd months after infection. All measurements were performed at the same time of the day (14:00–16:00 pm) to minimize the effect of circadian changes in the pupiller response. During the measurements, the subjects were advised to look straight ahead, not at the light source, to prevent the accommodative response. We performed all measurements after a dark adaptation interval of 5 min, which was followed by scotopic measurements at illumination of 0.4 lx, mesopic measurements at illumination of 4 lx, and photopic measurements at illumination of 40 lx. LED lighting was the only light source in the room, and the illumination conditions were tested and adjusted using a photometer. Then the pupillometry measurement started at the illumination of 500 lx, the measurement continued with the illumination switched off until the end of the session. Thus, this technique makes it possible to monitor pupil responses in conditions ranging from photopic to scotopic and to evaluate the pupil size and offset instant by instant (with pupil diameter measurements at 0th and 1st and every two seconds after 2nd) (Fig. 1). The following equation was used to calculate the speed of change in pupillary diameter. Average speed ($V_{\text{average-mm/s}}$) was the overall average speed until that time. Φ is the pupil diameter (mm) at the time of measurement. t_x is the second that the desired speed will be measured.

$$V_{\text{average}(t_x)} = [\Phi_{t_x} - \Phi_{t_0}] / t_x.$$

OD

Scotopic (0.04 lux):-0.17 mm,0.10 mm,6.30 mm
 Mesopic (4 lux):-0.18 mm,0.11 mm,5.55 mm
 Photopic (40 lux):-0.15 mm,0.19 mm,3.91 mm

Dynamic:
 $\varnothing(0)$:xc = -0.11 mm yc = 0.27 mm \varnothing = 4.02 mm
 $\varnothing(N)$:xc = -0.18 mm yc = 0.24 mm \varnothing = 5.56 mm

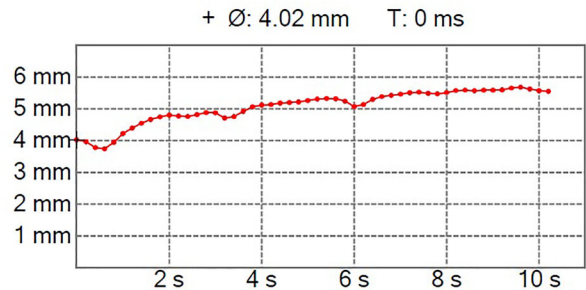
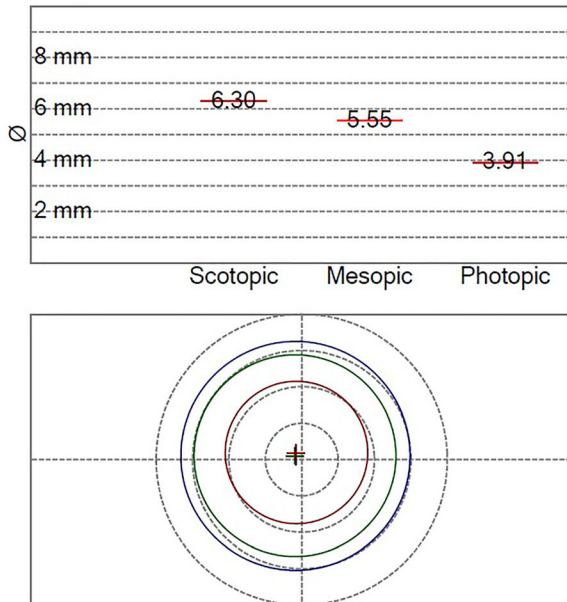


Fig. 1 An output of pupil response analysis of Sirius Topographer (CSO, Italy). The pupil diameters under different illumination conditions are shown and the legends indicate the centroid location (x, y) and pupil diameter on the left side of the

output graph. The right side of the graph shows the output of dynamic pupil response analysis and the legend indicates the centroid location (x, y) and the pupil diameter at a particular time

Statistical analysis

NCSS (Number Cruncher Statistical System) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The suitability of quantitative data to normal distribution was tested by Shapiro–Wilk test and graphical analysis. Paired sample t-test was used for comparing normally distributed quantitative variables between during active infection and 3rd months post-infection. Wilcoxon signed-ranks test was used comparisons of quantitative variables that did not show normal distribution. Pearson’s Chi-square test was used to compare qualitative data. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $p < 0.05$.

Results

The study was conducted with a total of 58 cases, of which 43.1% ($n = 25$) was female and 56.9% ($n = 33$) was male. The mean age was 47.23 ± 1.1 years. (range: 40–59).

Ptosis was not detected in any of the cases.

Table 1 shows comparisons of mean scotopic, mesopic and photopic diameters results for the bilateral eye. The mean scotopic and mesopic pupil diameter of COVID-19 cases was found statistically significantly lower than the results of 3rd months ($p = 0.001$, $p = 0.023$; respectively). No statistically significant difference was found in the mean photopic pupil diameter. ($p > 0.05$).

Figure 2 shows the pupil responses by the given time and comparisons of the results for the right eye. In bilateral pupil responses, there was no significant difference in terms of the pupil diameter with 500 lx at

Table 1 Evaluation of scotopic, mesopic and photopic static pupil diameters

| | | Groups | | | <i>p</i> |
|--------------|------------------|---------------|---------------|---------------|----------------------|
| | | Total | Covid-19 (+) | 3rd months | |
| RSCOTOPIC/mm | Min–max (median) | 2.5–6.9 (4.7) | 2.5–6.9 (4.1) | 2.9–6.7 (5.4) | ^a 0.001** |
| | Mean ± Ss | 4.7 ± 1.08 | 4.18 ± 1.03 | 5.19 ± 0.87 | |
| RMESOPIC/mm | Min–max (median) | 2.2–5.7 (3.8) | 2.2–5.7 (3.6) | 2.4–5.7 (4.1) | ^a 0.023* |
| | Mean ± Ss | 3.86 ± 0.85 | 3.68 ± 0.86 | 4.03 ± 0.81 | |
| RPHOTOPIC/mm | Min–max (median) | 2–5.4 (3.1) | 2–5.4 (3) | 2–4.4 (3.1) | ^a 0.438 |
| | Mean ± Ss | 3.22 ± 0.72 | 3.27 ± 0.83 | 3.17 ± 0.59 | |
| LSCOTOPIC/mm | Min–max (median) | 2.1–6.8 (4.3) | 2.1–6.1 (3.7) | 2.6–6.8 (4.9) | ^a 0.001** |
| | Mean ± Ss | 4.4 ± 1.09 | 3.92 ± 1.01 | 4.87 ± 0.96 | |
| LMESOPIC/mm | Min–max (median) | 1.8–6.2 (3.6) | 1.8–5.5 (3.4) | 2.1–6.2 (3.8) | ^a 0.046* |
| | Mean ± Ss | 3.71 ± 0.88 | 3.55 ± 0.88 | 3.86 ± 0.87 | |
| LPHOTOPIC/mm | Min–max (median) | 1.7–5.6 (3.1) | 1.8–5.3 (3) | 1.7–5.6 (3.1) | ^a 0.485 |
| | Mean ± Ss | 3.17 ± 0.72 | 3.22 ± 0.79 | 3.12 ± 0.65 | |

Min Minimum, *Max* maximum, *SD* Standart deviation, *COVID-19* Coronaviruse disease 2019

^aStudent-*t* Test-^{*}*p* < 0.05, ^{**}*p* < 0.01

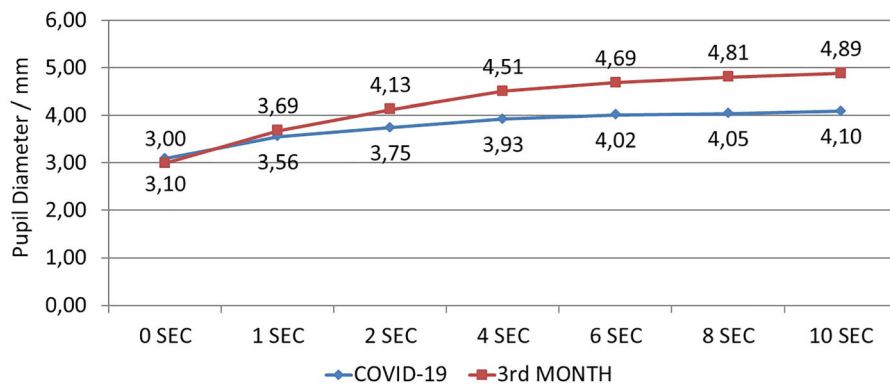


Fig. 2 The dynamic pupil response by the given time and comparison of the results. *Sec* second, *mm* millimeter

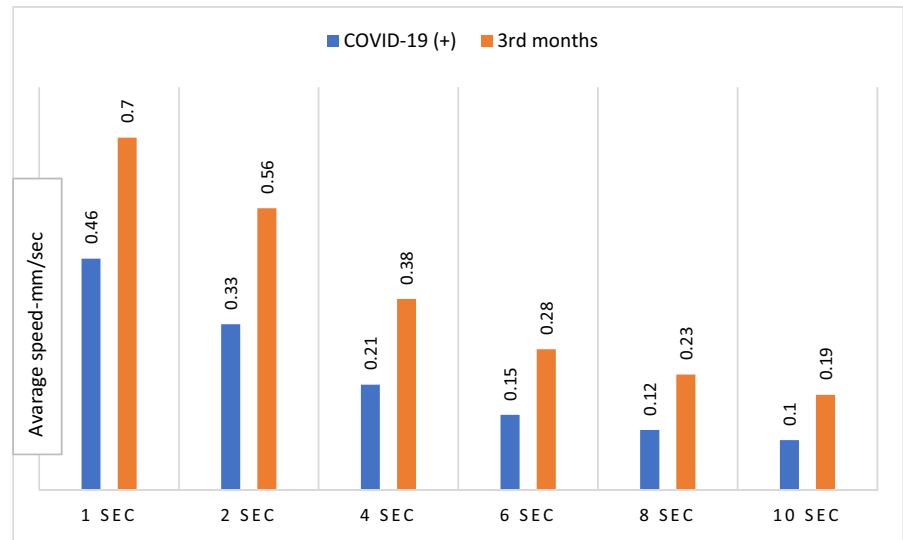
0th seconds ($p = 0.734$). The bilateral pupil response analysis revealed that the mean pupil diameter was significantly lower in active COVID-19 infection than results of 3rd months at the 1st, 2nd, 4th, 6th, 8th, and 10th seconds. ($p < 0.01$ for each).

Figure 3 shows the distribution of dilation speed measurements according to time for the right eye. The average speed of bilateral pupillary dilation was statistically significantly lower in active infection of COVID-19 than the results of 3rd months after infection at the 1st, 2nd, 4th, 6th, 8th, and 10th seconds ($p = 0.001$; $p < 0.01$ for each).

Discussion

SARS-CoV-2 is a highly infectious virus associated with significant morbidity and mortality [9]. There may be also autonomic system involvement in COVID-19 infection [9]. The pupil response is controlled by both the parasympathetic and sympathetic systems [11]. The evaluating pupil's responses with different standardized light intensities may be used to detect autonomic dysfunction [12, 13]. In this study, we have aimed to compare the results of the pupiller responses in COVID-19 cases with the results of 3rd months post-infection to detect if there is any

Fig. 3 Distribution of average dilation speeds according to time. *Sec* second, *mm* millimeter



effect of COVID-19 infection on the pupillary reactions.

Appropriate pupil response requires functional and robust neural pathways. Pupillary diameter is controlled by two muscles, the sphincter pupillae, which is primarily under the control of the parasympathetic nervous system, and the dilator pupillae, which is primarily under the control of the sympathetic nervous system [14]. We found the mean mesopic and scotopic diameters significantly lower during active COVID-19 infection compared to the 3rd months after infection. We also did not see a significant difference in mean photopic diameter during active COVID-19 infection compared to 3rd months after infection.

Reflex pupil dilation after the termination of light is comprised two components: (1) inhibition of the preganglionic parasympathetic nerve activity originating from the EW nucleus causing a decrease in iris sphincter tone and (2) an accentuation (“turbocharge”) of dilation from reflex increase in sympathetic nerve activity stimulating the iris dilator muscle [15]. The sympathetic component of peripheral nerve activity increase is most active during reflex dilation from the period from 5 to 15 s after the light is terminated [15]. In our study, no significant difference was detected in pupil diameter at 0th seconds as contraction amplitude during active COVID-19 infection and 3rd months after infection. However, the mean pupil diameter was significantly lower at all the seconds measured reflex pupil dilation during active

COVID-19 infection compared to 3rd months after infection.

The average speed of pupillary dilation was statistically significantly lower at all seconds at reflex pupil dilation during active COVID-19 infection compared to 3rd months after infection. These findings support that there is dilation lag.

Inferring under or overaction of sympathetic and parasympathetic nerve activity based on static measurements of steady-state pupil size in patients where any expected differences from age-matched normal are assumed to be affecting both right and left pupils is very difficult. This is because many factors can affect steady-state pupil size and reflex dilation besides peripheral parasympathetic and sympathetic nerves. However, the most common factor that can affect pupil size is the degree of central inhibition of the right and left Edinger-Westphal Nuclei. These inhibitory fibers originate from reticular activating formation and the locus coeruleus and ascend in the brainstem in the periaqueductal gray to innervate the right and left EW nuclei [16]. In many CNS states, including systemic illness, the inhibition is often less, resulting in smaller pupils in darkness or in dim lighting conditions. In our study, all these findings may be caused by less inhibition of parasympathetic nerves or bilateral sympathetic denervation. Ptosis is expected in sympathetic system dysfunction [17]. However, we did not detect ptosis in the cases. And also in the case of bilateral sympathetic underactivity, it is very difficult, if not impossible to differentiate a slow reflex dilation

due to sympathetic under-action vs. disinhibition of the EW nucleus centrally due to the status of CNS activity of the ascending inhibitory fibers [18]. In such cases, most people rely on the apraclonidine test to diagnose a sympathetic deficit (the alpha-1 receptor supersensitivity requires about 48–72 h to occur for an apraclonidine test to show dilation after 30–50 min). Even apraclonidine testing can be equivocal in the case of bilateral small pupils because some normal eyes show dilation and not miosis after application of apraclonidine [19]. We did not do the aproclonidin test. Therefore, it would not be correct to make a definitive conclusion about the etiology of these study results.

However, all comorbidities associated with increased morbidity/mortality in COVID-19 are characterized by sympathetic overactivation [20]. We did not include cases with comorbidities in this study, so we may not have detected sympathetic overactivity. COVID-19 may also further increase sympathetic discharge through the change in blood gases as in chronic intermittent hypoxia [20]. Another reason why we could not detect sympathetic excessive activity in our study may be that our cases were not hypoxic. COVID-19 may also activate the sympathetic system through increased production and release of AngII [20]. However, in our study, the pupillometry results did not correlate with this hypothesis. The possible cause of this may be direct neuroinvasion of the virus. Because the ACE-2 receptors that Sars-Co-2 virus enters the cell with are also present in the central nervous system [5, 21, 22].

Unlike the results of our study, there are case reports with a tonic pupil thought that might be associated with COVID-19 [23–25]. This can be explained with the fact that the clinical course of COVID-19 might be characterized by individual differences. There is also another study measured that the various parameters of the pupil responses of critically ill patients with COVID-19 and compared these parameters with those of patients with respiratory failure of different etiology. They found pupillary light reflex measurements were not significantly different between intensive care unit patients treated for COVID-19 and patients with respiratory failure of different causes [16]. Unlike the results of our study, the lack of significant differences in pupillary response in COVID-19 cases may be due to the different characterization of COVID-19 at different stages.

Further studies are needed to clearly understand the pathogenesis.

To date, it is still controversial if the ocular surface could be a way of access for COVID-19. The eye surface and the nasopharyngeal mucosa are the exposed surfaces amenable to contagion because they express ACE2 receptors. Therefore, the eye could be the first entrance door, then diffusing into the nose and throat, or a secondary event, further to the nose infection. In this view, it is possible to assume a direct primary viral involvement of the autonomic nervous system involvement starting from the eye and then proceeding centrally [26, 27]. Some authors have reported that SARS-CoV-2 disease may be characterized by ocular manifestations (including conjunctivitis), which may present as the initial and the only symptom of infection. In this perspective, the examination of brainstem reflexes such as corneal reflexes and pupillary reflexes may play an early sign of CNS involvement and be used in the routine screening of affected patients.

One of the limitations is the device we used to measure pupil responses did not measure the contraction speed. This might have caused a deficiency in the interpretation of the results of this study. The device we used cannot take measurements of both eyes at the same time, this can be considered a disadvantage. A portable pupillometry device, which only measures the pupillary response, maybe a more appropriate option.

In conclusion; the present study showed that pupil responses show significant differences in during active COVID-19 infection when compared with the measurements of 3rd months after infection. It must be kept in mind that the clinical course of COVID-19 is characterized by different phases and individual responses. The potential role of the COVID-19 on the autonomous nervous system will have to be investigated by further prospective studies.

Declarations

Conflict of interest The authors declared that they have no conflict of interest.

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